# U.S. EPA NEW APPROACH METHODS (NAMS) WORK PLAN WORKSHOP

**Workshop Summary**
January 29, 2020
U.S. Environmental Protection Agency
Arlington, VA

## Welcome and Charge to the Group

Sarah Stillman (EPA, Office of Chemical Safety and Pollution Prevention [OCSPP]) welcomed everyone to the workshop and introduced Alexandra Dunn (Assistant Administrator of EPA's OCSPP). A. Dunn greeted attendees and thanked everyone for traveling to this much-awaited workshop. A. Dunn noted that scheduling this follow-up to December's workshop allowed time to think, reflect, and cogitate on the initial meeting. The December workshop summary is long and gives a great starting point. A. Dunn extended appreciation to her Office of Research and Development (ORD) colleagues, especially David Dunlap (Deputy Assistant Administrator for Science Policy), for working collaboratively. Today, people from other EPA offices (Office of Water [OW], the Office of Air and Radiation [OAR], and the Office of Land and Emergency Management [OLEM]) are bringing an Agency-wide perspective.

A. Dunn met with Administrator Andrew Wheeler the day before, and it went well. She sent him home with today's agenda and told him of the group's commitment to implement his NAMs goals. He was glad to see the progress. This initiative is important to him, and in this group, we share that enthusiasm and bold vision. We can use NAMs to reduce animal testing and to gather better and more current information on hazards and exposures. We are excited and anxious to let the Administrator know how today's workshop goes and to report progress on the work plan to meet the goals and deadlines in his memorandum.

A. Dunn charged the group with thinking about what that work plan will look like and not to be daunted by its delivery. Think of how to promote transparency, good science, environmental soundness, and animal reduction. She listed questions to consider:

- What is our baseline?
- What are we going to measure and report, and how?
- How do we encapsulate this goal as an Agency but also in different offices?
- What's the state of the science?

External stakeholders want to be engaged with the Agency. We will be thinking about continued involvement of people outside this room. We did a great job of making the December workshop a public opportunity. People will be interested in our journey and maybe even this work plan, so we want to think of how to engage others. We also need to realize that some choices are ours as an Agency, and third parties may have other ideas of how to do things.

Today you will be addressing difficult questions like validation and variability in methods and the flexibility of current statutes and regulatory requirements. A. Dunn emphasized that this project will take multiple years. She thanked the scientists for their dedication to making the Agency a beacon of great ideas and noted that other agencies and nations may emulate EPA. A. Dunn mentioned the progress the Agency has already made in reducing animal testing and looked to the future to continue to improve.

A. Dunn recalled visiting zebrafish, Petri dishes, and more in EPA labs and their illustration of NAMs' potential. She emphasized that the Agency will move forward boldly and with scientific integrity. Some changes will be more incremental and longer-term, requiring long-term energy from the Agency. A. Dunn encouraged the group to consider how to use the Agency's tools, resources, advisory boards, and standing panels. Anna Lowit (Senior Science Advisor,

Office of Pesticide Programs [OPP]) has given ideas on how to use the Science Advisory Board (SAB), a thoughtful, deliberative body. The SAB has a long horizon, a year or two, to work on things and some NAMs-related work may be perfect for that.

A. Dunn encouraged the group to build support for its goals with integrity and emphasis on the gains associated with moving towards NAMs. She introduced Rusty Thomas (Director of EPA's Center for Computational Toxicology & Exposure, ORD) for a recapitulation of the successful December workshop.

## Recap from the First Annual NAM Conference

*Rusty Thomas (EPA-ORD) presented a recap of the December meeting.*

- R. Thomas thanked Alexandra Dunn for opening the workshop today and for delivering an inspirational charge.
- R. Thomas commented that most of what he covered is in the Summary Report from the December meeting.
- Monica Linnenbrink will be sending out a link to the slides from all the presentations from the December meeting for review as needed or wanted.
- R. Thomas summarized Anna Lowit's (EPA-OPP) presentation:
    - A. Lowit touched on the need to establish baselines for current animal use in EPA. If we don't measure it, we can't improve it. Where are we now, and where do we need to go?
    - Each EPA office uses animal tests for different reasons and will report in different ways. We will need to harmonize tracking between different programs and groups.
    - EPA has already reduced animal testing by 50% over the last three years, so the Administrator's goals of another 30% by 2025 should be attainable.
    - OPP submissions typically use anywhere from 20,000 to over 100,000 animals each year.
    - OPP's use of HASPOC waivers has already reduced animal testing and has saved about 200,000 animals over the last 6.5 years.
    - The OPPT strategic plan to promote the development and implementation of NAMs in TSCA included a retrospective analysis of required information under TSCA where animals are currently used. This retrospective analysis is nearing completion, and the results should be helpful in guiding where the best targets for animal use reduction may be.
    - The ongoing cross-cutting programs with NICEATM, OECD, and other groups need to be considered. We want to be the ones out front and leading, but it is best to also bring stakeholders and partners together as we move forward.
- R. Thomas summarized Thomas Monticello's presentation:
    - T. Monticello presented as a representative of the IQ Consortium. His research focused on the concordance of animal (pre-clinical) testing and human results.
    - The IQ Consortium developed a prospective, blinded database of 182 molecules with animal toxicology together with human Phase I clinical data.
    - It is difficult to compare pre-clinical data to human data as you may not see chemicals that were identified as toxic in animals ever making it to humans.
    - T. Monticello discussed positive and negative predictive value.
        - He placed most emphasis on positive and negative predictive value since they are more aligned with non-clinical to clinical translation.
        - The positive predictive value was generally less than 30% for rodents and about 45% for non-human primates, demonstrating poor concordance and a poor ability to predict the presence of a health effect.
        - The negative predictive value overall had a very high value (85-90%) which means that, generally, the current preclinical (animal) tests do a good job of predicting the absence of health effects.
        - The conclusion was that current animal models do a better job at predicting 'safety' (i.e., the absence of an effect) than specific hazards.
- R. Thomas summarized Nicole Kleinstreuer's presentation.
    - NICEATM has been leading the way, with EPA, in researching variability.
    - The qualitative reproducibility of animal hazard data is generally from 70-80%. About 30% of the time, you would get a different answer if you ran a study more than once.

  - For potency categorization in eye irritation, the reproducibility is dependent on its potency category. The extremes are reproducible, but the middle of the range is harder to reproduce.
  - In acute oral toxicity tests, the 95% confidence interval for LD50 values are generally $\pm$ 0.3 $\log_{10}$ units with highest variability in the high EPA hazard categories.
  - For skin sensitization, NAMs perform as good as or better than animal models – hazard (74% vs 80%), 3 class potency (59% vs 60%).
- R. Thomas summarized Katie Paul Friedman's presentation:
  - EPA ORD developed a curated database of legacy animal toxicity studies (ToxRefDB) that currently contains >5000 studies on >1000 substances.
  - Applied multiple statistical approaches to evaluate the quantitative variability in repeat dose animal studies.
  - Maximal R-squared for a NAM-based predictive model of systemic effect levels may be 55 to 73%; i.e., as much as 1/3 of the variance in these data may not be explainable using study descriptors.
  - The estimate of variance (RMSE) in curated LELs and/or LOAELs approaches a 0.5 log10-mg/kg/day.
  - Estimated minimum prediction intervals for systemic effect levels are likely 58 to 284-fold based on RMSE estimates.
  - The current LOAEL-NOAEL uncertainty factor ($UF_L$) (i.e., 10-fold) covers the estimated one-sided minimum prediction interval.
  - The bottom line was that depending on what your analysis is, the results could be variable.
- R. Thomas summarized Dave Allen's presentation:
  - The "six pack" of acute toxicity studies is generally well known by OPP, but other groups may not be as familiar.
    - Includes acute oral, acute dermal, acute inhalation, skin irritation, eye irritation, and skin sensitization with total animal numbers ranging from 36 – 86 animals.
  - Retrospective studies showed that the acute dermal studies offer little additional data, so waivers can be issued.
  - A consensus QSAR model was able to be developed that performed equally as well as in vivo models when variability was considered by curating acute oral toxicity data.
  - Acute inhalation data is being curated and 3D in vitro models are being evaluated.
  - NAMs for skin and eye irritation are being tested for performance.
  - Defined approach for skin sensitization working its way through OECD.
- R. Thomas summarized Tara Barton-Maclaren's presentation:
  - Explained how Health Canada is using NAMs in application to quantitative level screening risk decisions.
  - The Chemicals Management Plan (CMP) is a program to reduce the risks posed by chemicals to Canadians and their environment. In Phase 3, 1550 priority chemicals out of the original 4300 chemicals will be addressed by 2020. Many of the chemicals do not have traditional animal toxicity data.
  - Health Canada showed a Scientific Approach Document (SciAD) that outlines specific scientific approaches which can be used in future assessments or prioritization.
  - They developed a case study around a SciAD demonstrating that in vitro bioactivity form ToxCast provides a conservative estimate of a point-of departure from traditional animal toxicity studies.
  - They began applying this in a risk-based manner to their priority chemicals and showed that this method showed that the bioactivity-to-exposure ratios (BER) for a subset of chemicals were generally aligned with CEPA 6(c) assignments and will be used to inform priority compounds under the CMP.
  - Health Canada is developing preliminary uncertainty factors (UFs) to apply to screening level assessments based on in vitro bioactivity.
  - They are working to expand the approach by using bioactivity from nearest neighbors and in silico toxicokinetic estimates.
    - Useful for chemicals that do not have bioactivity data, improving read-across and more.
- R. Thomas summarized George Daston's presentation:
  - Described the state of the science on developmental and reproductive NAMs.
  - Current animal tests are a bit of a patchwork to cover the whole reproductive cycle as no one test

covers it.
    - The current NAMs only cover a very small part of the cycle. Necessitating either a patchwork of NAMs or a need to expand the current NAMs to cover the whole cycle.
    - The 2017 National Research Council Report suggests combining cheminformatics, pharmacokinetic models, systems biology, and mechanistic models into a predictive toxicology workflow to identify acceptable doses for untested substances.
    - The predictive toxicology workflow relies heavily on read across as the primary method for assessing developmental and reproductive toxicants on a broad basis.
    - A range of in vitro assays exist for developmental studies including whole embryo culture, stem cell assays, and free-living embryos (zebrafish).
    - Discussed criteria for believing in a NAM
        - Covers a defined range of modes of developmental tox
        - Integrated with other assays to comprehensively cover all potential modes of action for dev tox
        - Responsive to human developmental toxicants with dose concordance
- R. Thomas summarized Dan Tagle's presentation
    - State of the science in tissue on a chip technology.
    - Microfluid cell type cultures that mimic the 3D morphology and physical properties of a tissue.
        - For example, you need that stretching in lung cells in order to keep cells operating as though they were in the real organ.
        - A number of organ platforms exist, from skin, to the gastrointestinal system, nervous system, liver, kidney and more. On a liver chip, for example, the middle of the chip includes hepatocyte cells and non-parenchymal cells to recapitulate aspects of liver function, and a flow culture allows for transport. Toxicity can be measured using imaging and staining.
    - Organs on a chip are designed to be modular and can be linked together, as demonstrated by a group from Pittsburgh that linked the blood brain barrier, liver chip, and other organs together.
    - NIH, FDA, and DARPA helped develop the first research. Partnerships have now included groups such as NASA.
    - Added validation groups to ensure that the tissue chips are reproducible and transferable.
    - Initiatives at NIH for further development include representing as much of the population demographics in the chips as possible, working towards building a human body on a chip and addressing drug failure rates.
- R. Thomas summarized Doug Wolf's presentation:
    - Syngenta developed in vitro models for evaluating respiratory irritants.
    - Even though a sub-chronic whole animal inhalation study is a regulatory requirement, Syngenta did not feel that it was necessarily helpful to establish human health risk. Therefore, they worked with EPA to develop a NAM suitable to inform inhalation toxicity.
    - Particle size distributions and aerosols were evaluated during pesticide applications.
    - Airway dosimetry was estimated using computational fluid dynamic (CFD) modeling.
    - A 3D model of the human airway epithelium from 5 different donors were exposed for 24 hours at 10 different concentrations. The data was then combined with uncertainty factors to show how it could relate to a whole animal study.
    - Measured trans epithelial electrical resistance, LDH, and resazurin.
    - BMD modeling identified a human equivalent concentration.
    - The approach addressed the requirements of an inhalation study without killing animals and addressed uncertainty factors as well.
- R. Thomas summarized Maureen Gwinn's presentation:
    - M. Gwinn presented on endocrine disrupting chemicals using in vitro and computational approaches.
    - Food Quality Protection Act and Safe Drinking Water Act require evaluating 10,000 substances for potential endocrine activity. This testing requirement is very expensive and uses a lot of animals.
        - The Endocrine Disruptor Screening Program (EDSP) established a two-tiered system to evaluate chemicals. Tier 1 uses ~600 animals and costs ~$1 million.
    - Using high-throughput assays and computational models, an approach was begun in 2011 to screen these chemicals more efficiently.

  - Multiple high-throughput screening assays used to screen chemicals for estrogen and androgen receptor pathway activation with computational modeling used to integrate the data. Reference chemicals used to characterize the performance of the computational model/assays.
  - Consensus QSAR models developed for ER and AR agonism/antagonism.
  - Lessons learned included understanding the impact of cytotoxicity on assay results, the utility of developing models from a subset of assays, the impact of metabolic competence on assay results, and need to quantify uncertainty.
  - Additional activities under EDSP include developing a model for steroidogenesis and thyroid.
- R. Thomas summarized Warren Casey's presentation:
  - NICEATM – New approaches to validation and Characterizing Performance.
  - The traditional validation model is based on OECD GD 34 and does not work. Issues include segregation of steps, which causes a lot of time and effort to be wasted.
  - When thinking about validation, we want to develop a flexible validation approach that focuses on the end user. In doing this, you will develop a method that fits the need of regulatory agencies and the industry.
  - Need to include institutional resistance and needing to establish what are we validating against.
  - Also need to harmonize across different regulatory jurisdictions. Transition from a centralized process from a one size fits all to a fit for purpose approach. Also moving away from "validated or not" and moving into "does this have the appropriate level of scientific confidence for what I need."

*R. Thomas paused here for questions*

- **Susanna Blair (EPA-OPPT):** Did you feel as though there was anything big that wasn't captured at the conference?
  - **R. Thomas:** No one had any specific things, but Rusty commented that it was difficult to discuss everything that could be needed to develop this work plan, but there was enough to move forward. Some areas may need greater depth in the future.
- **David Bussard (EPA-ORD):** Thank you Rusty for the recap as being there for the whole day, your mind sort of hits a wall on what it can process.

*R. Thomas gave an overview of what was discussed in each of the December breakout groups:*

- R. Thomas commented that he appreciated the work of ICF in being able to record the discussions and tangents that were in each Subgroup. The Subgroups today will be able to incorporate their potential concerns and thought processes and that is very important. The Subgroups today should review their discussions and make sure that they are incorporated as possible.

Breakout Group #1: Variability and Relevance of Current Animal Tests and Expectations for NAMs

- **Question #1:** The amended TSCA legislation states that NAMs should provide "information of equivalent or better scientific quality and relevance" than the existing animal tests. How should the scientific quality and relevance of the existing animal tests be evaluated to set the appropriate benchmarks for NAMs? What additional research, if any, is needed to help define these benchmarks?
  - NAMs should be evaluated for human relevance and quality, and not against the animal tests. The animal tests themselves may not be the best reference as certain toxicities can be missed (e.g., drug-induced liver injury, cardiotoxicity) or mechanisms seen in animals are not relevant to humans.
  - Existing animal tests can be evaluated quantitatively to better understand how NAMs compare in terms of performance and predictivity. If we better characterize uncertainty and variability in animal studies, we can more accurately benchmark performance of NAMs.
  - Additional research could include working to understand the disease states of interest to develop NAMs (autism etc.) and increasing the use of electronic database submission so animal testing data can be evaluated.
- **Question #2:** Emerging evidence suggests that that traditional toxicity studies are better at identifying the absence of an effect (i.e., negative predictive value) than accurately identifying specific adversities. How could this evidence influence the expectations on the use of NAMs in toxicity testing?
  - NAMs seem to have the ability to pick up biological responses potentially at a lower dose than the animal tests.

  - The absence of an effect in a NAM does not mean the same thing as in animal studies, as bioactivity can be measured that may not represent an adverse outcome. Negative results from NAMs sometimes indicate that the dose-response range was too low.
  - If there is value in using animal studies to measure the negative predictive value, then we should define the context in which those studies would be useful.
  - Discussions around NAMs should be endpoint-specific and we should be wary of generalizing across all NAMs.
- **Question #3:** How can information on the variability and relevance of the current animal testing approaches be collected and communicated without undermining confidence in the standard risk assessment paradigm where whole animal studies are used to identify specific hazards and derive points of departure?
  - Analyses presented today showed variability in acute toxicology studies led to a 0.3 log confidence interval around quantitative LD50s, and variability of subchronic/chronic studies found a 0.3-0.5log CI, which is consistent with the 100x UFs that have been used in traditional risk assessments and shows that approaches have been health protective.
  - Lessons learned around the reproducibility of in vitro tests should be used to inform NAM development and expectations.
  - Animal tests can be used to inform what dose ranges are relevant for in vitro assays.
  - We should work towards better understanding the domain of applicability of animal studies (where they are good and where they are weak) and discuss how NAMs compliment those studies.

Breakout Group #2: State of the Science in Development and Application of Alternatives

- **Question #1:** Identify NAMs which are close to being fully developed or are ready for regulatory use/application, and for what decision contexts they are being used (i.e., prioritization, qualitative assessment, quantitative risk assessment).
  - Skin sensitization is very close to being used across all contexts. It is currently being used for qualitative risk assessments.
  - Replacements for the six-pack are far along in development as well, though the replacements can help with binary classifications and not necessarily quantitative or nuanced understanding of toxicity.
  - Some things labeled "NAM" are already well accepted and ready for use (e.g., read across, QSAR).
  - NAMs don't need to be mapped to one adverse endpoint.
  - The contexts listed pre-suppose the goal of identifying toxicants as opposed to safety, and it might be worth considering predicting safety as NAMs might be more appropriate for that.
  - NAMs should not necessarily be considered only in terms of a decision context, as it's possible that they can be used in combination with other data for various contexts.
  - Exposure should be a driver of interpretation of NAMs.
- **Question #2**: Considering any current or proposed regulatory use of NAMs (at US EPA or by other organizations), what are the near-term opportunities for application of existing NAMs in chemical risk assessment and/or regulatory decision making?
  - Implementation of existing approaches such as BMD, IVIVE, and other data could reduce animal testing now. Specific examples include using BMD modeling in toxicogenomics studies and using QSAR models for acute toxicity.
  - Using human-relevant data from NAMs could preclude the need for an interspecies uncertainty factor.
  - We should consider how a NAM-derived POD would be used in risk assessment – will it be a driver to collect more data or can it be used for decision making?
  - Education and comfort level around the use of NAMs will increase acceptance of them.
  - Will we accept POD NAMs if they are more conservative than what we have now? It must be an acceptance across the board.
- **Question #3**: What are the longer-term needs in the development or refinement of NAMs to maximize reductions in animal use? For which endpoints is there a regulatory need for NAM development?
  - Work to replace the methods that require the most animals (e.g., DART, studies that are conducted hundreds of times per year).
  - Work to replace the methods where you are most likely to have success using NAMs.
  - Specific endpoints include:

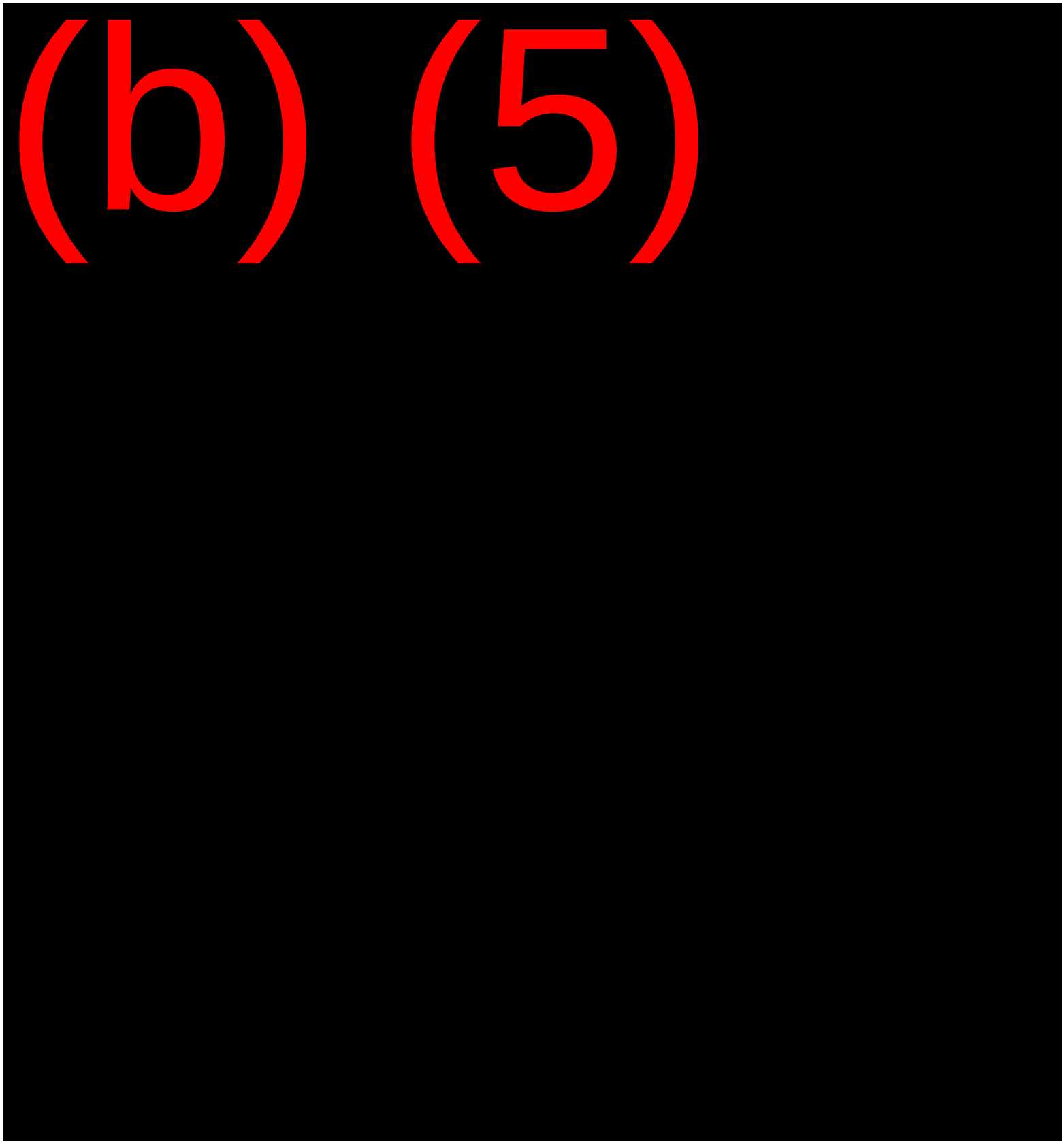
        - Reproductive endpoints, and specifically in the testes
        - Toxicokinetics
        - High throughput in vitro metabolism screen
        - Developmental neurotoxicity
        - Non-regulatory endpoints like autism, obesity
    - Other long-term needs:
        - Rapid exposure measurements and approaches
        - Understanding of how to measure toxicity of mixture
- **Question #4**: What are the benefits and/or detriments of applying NAMs that characterize the bioactivity of environmental chemicals versus identifying specific target organ or hazard for different regulatory contexts?
    - A bioactivity value can be used differently than a NOAEL in decision making, but what bioactivity means is a concern.
    - We need good coverage of the biological landscape with NAMs to adequately detect the most sensitive responses; if the coverage is sufficient, then mapping to specific target organ adverse responses may be unnecessary, depending on the regulatory context.
    - If NAMs are being used at relevant exposure levels, they need to be sensitive enough to detect subtle effects.

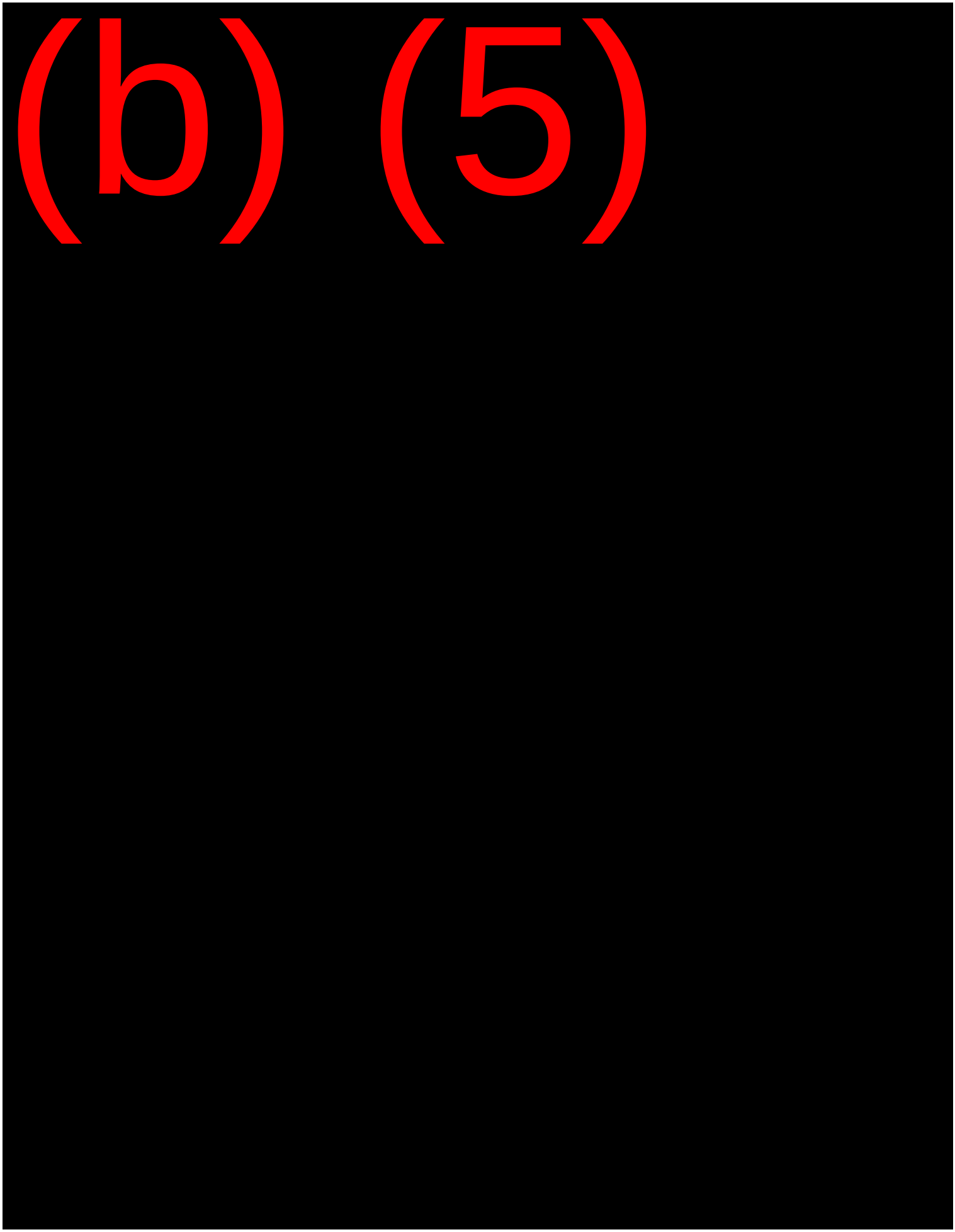
Breakout Group #3: Developing Scientific Confidence in NAMs

- **Question 1:** The historical approach to validation of NAMs generally follows OECD GD34 guidance, which involves multi-lab ring trials, a significant investment of resources, and multiple years to complete. Is the traditional approach to validation suitable to support both the rapid advances in NAM development and a full replacement of animal testing over the next fifteen years? If not, how must the concept of validation evolve to meet these needs?
    - This historical approach required extensive resources and time which may not be viable for NAM validation.
    - Validating if an assay measures what it is supposed to be measuring and if an assay can be performed reliably are different questions and can be pursued separately. The latter is not unique to NAMs.
    - Case studies are an effective approach for building confidence.
    - Validating with known biology (negative and positive controls) and showing concordance across various measurements can increase confidence.
- **Question 2:** Some approaches and frameworks to establishing scientific confidence propose a fit-for-purpose evaluation of NAM reliability and relevance. Can these more contextual approaches be sufficiently standardized to assure acceptance across multiple regulatory jurisdictions? If yes, how?
    - Because fit-for-purpose applications can be so varied, a structured framework helps build confidence and acceptance of methods.
    - Current validation methods can be considered fit-for-purpose, as different entities apply different standards.
    - Building consensus on what is feasible will take time.
- **Question 3:** As part of traditional validation efforts, the results from NAMs continue to be compared against results from laboratory animal studies. This poses a significant challenge since, in many cases, the laboratory animal studies themselves were never validated for their predictive capacity or assessed for reproducibility and transferability in ring trials prior to implementation as commonly done for NAMs. As such, NAMs are held to a higher data quality standard than the laboratory animal studies. Is this approach appropriate? If so, under what circumstances? If not, what is/are other approaches to building confidence in NAMs and ensuring that they are fit-for-purpose?
    - Tying NAMs back to animal results may not always be warranted.
    - However, animal data has a role in classification or other regulatory applications still.
    - Understanding AOPs can help determine which animal results are useful for validation.
- **Question 4:** Building scientific confidence in NAMs involves multiple considerations including a transparent description of the methods as well as the ability for an independent evaluation by third parties. However, some of the advances in NAMs use proprietary technology or limit the type of access by third parties. Can scientific confidence be established for NAMs that utilize proprietary technology while still maintaining the

confidential business information of developers? If so, how?

- Non-proprietary tests and transparency of methods are needed.
- Testing with reference materials or standards for performance or evaluation could help with this and is not different from how results from animal models are evaluated.

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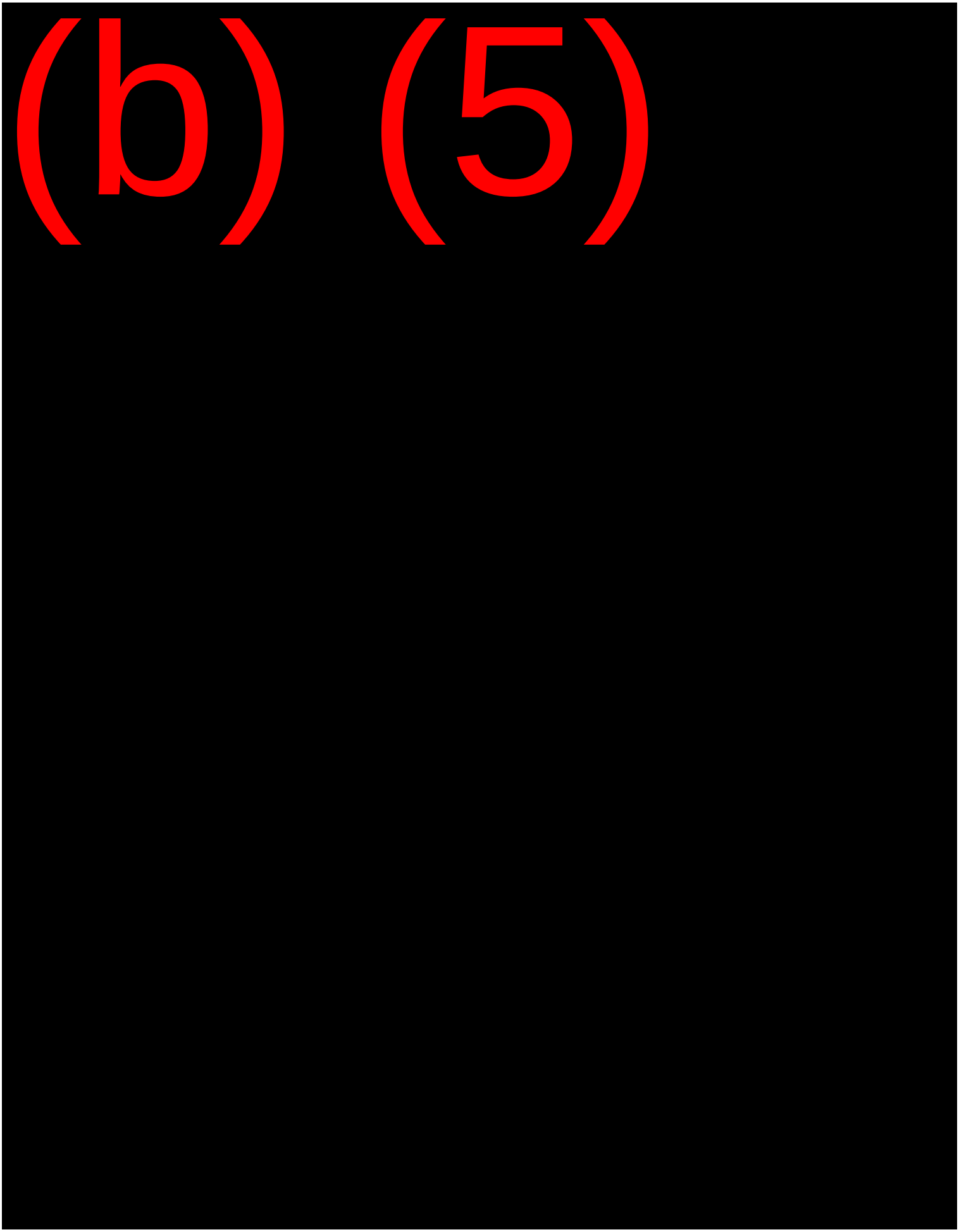
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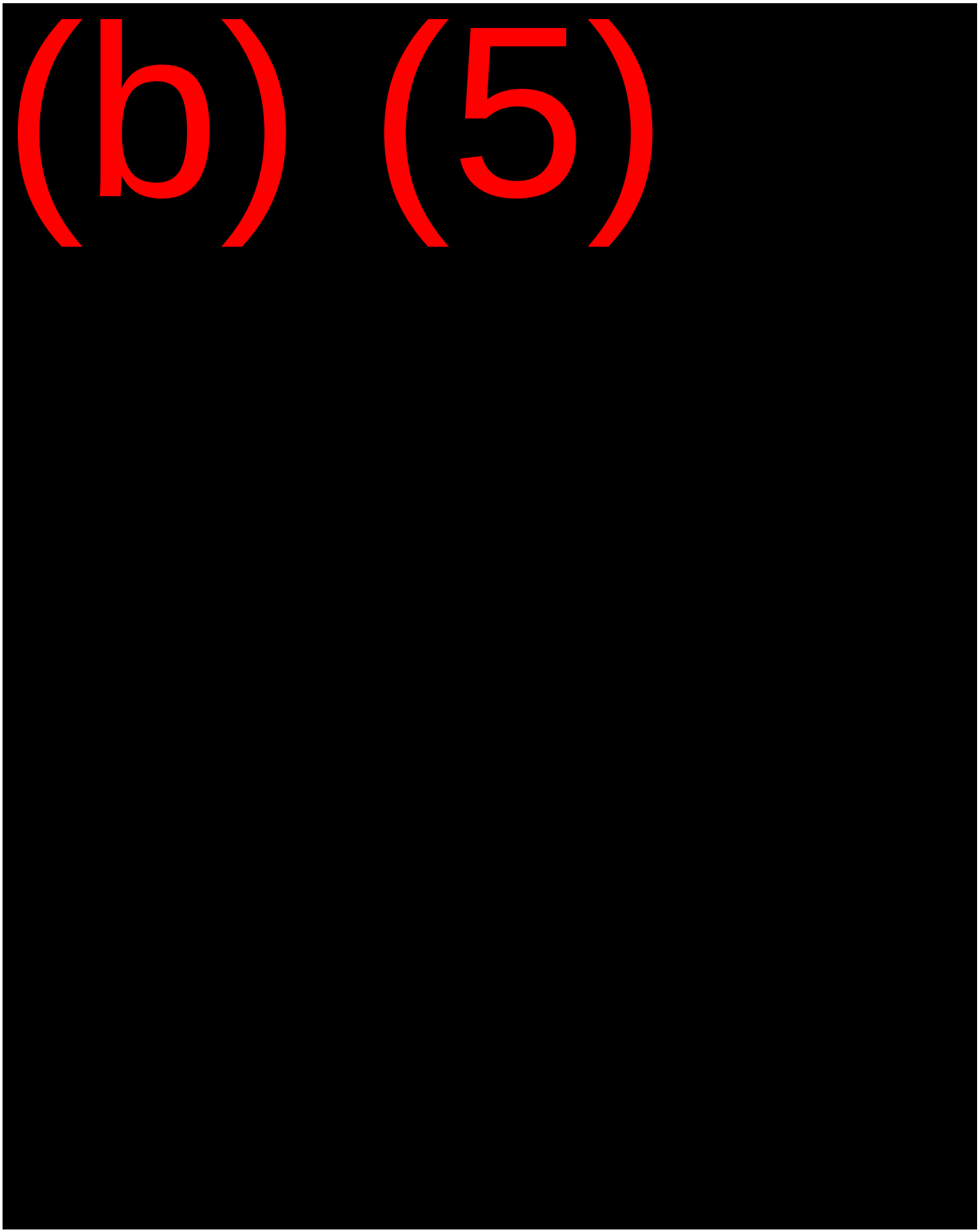
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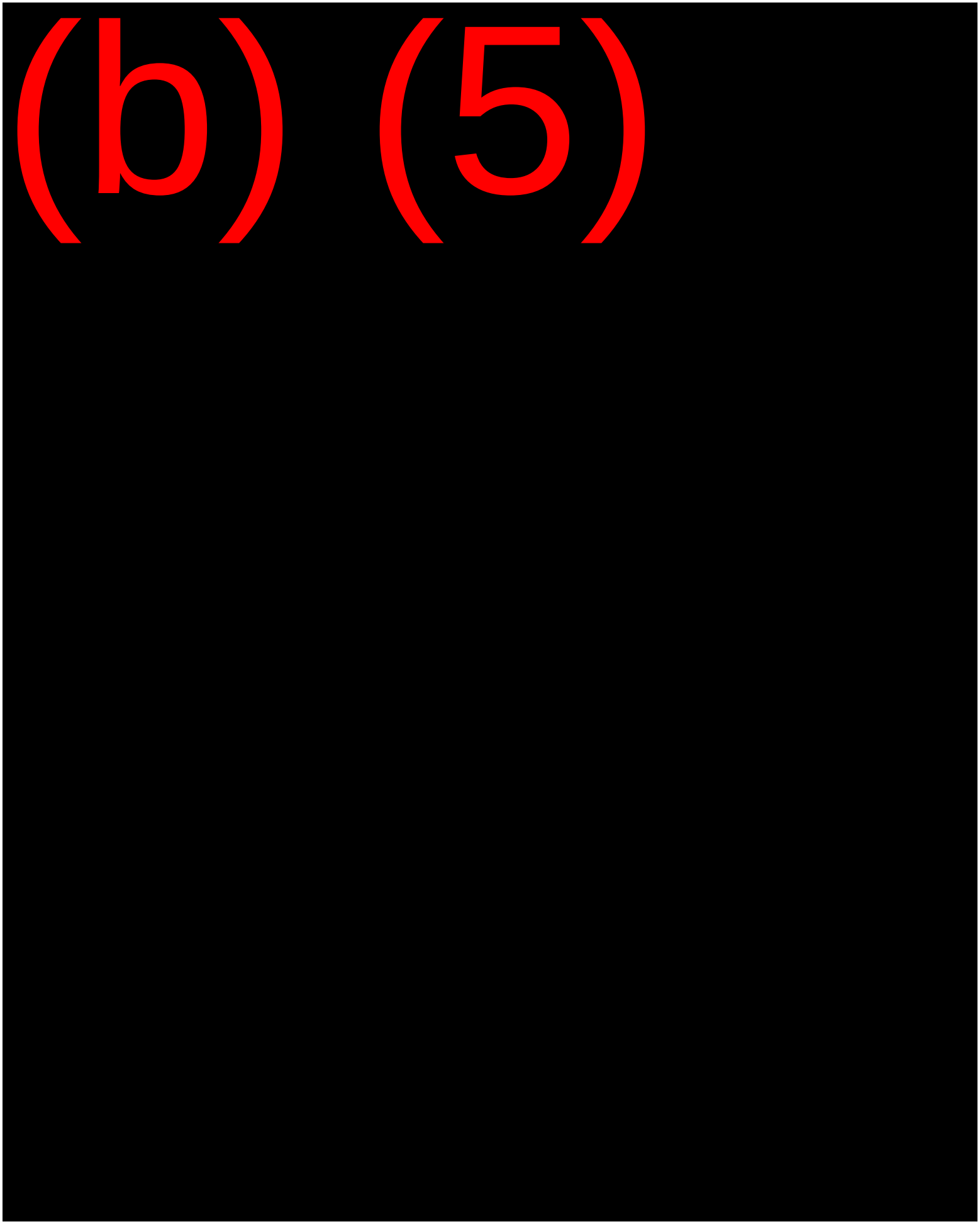
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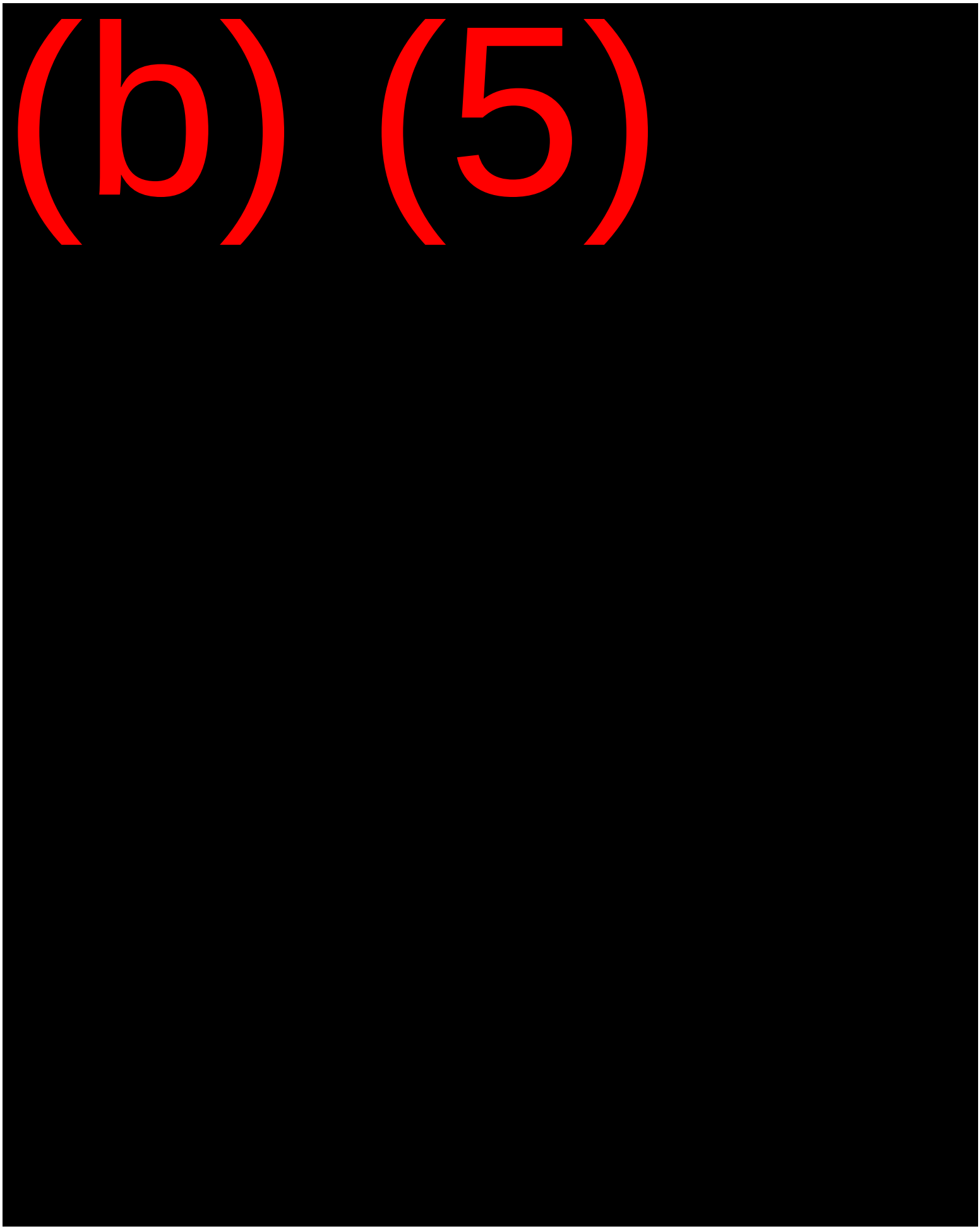
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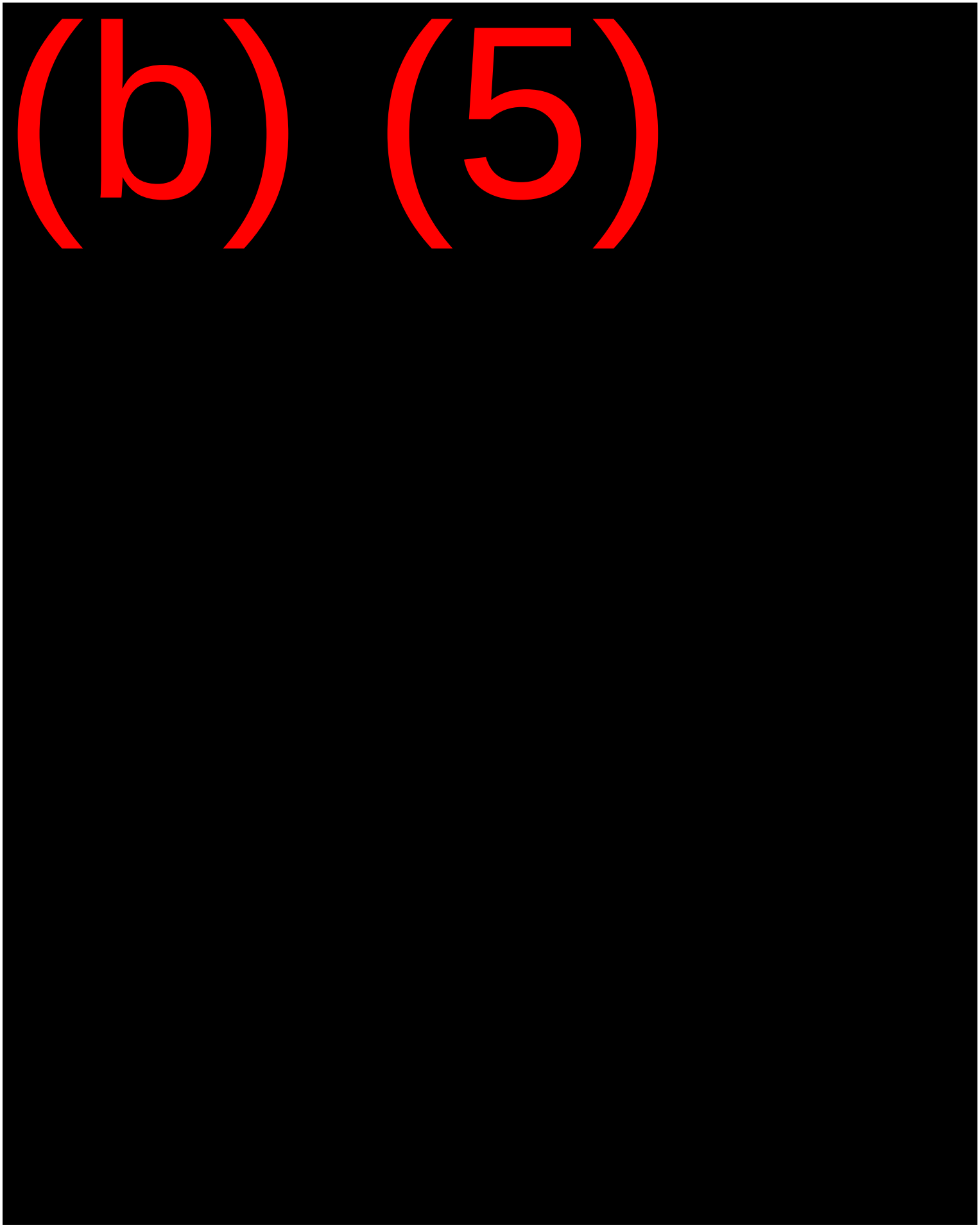
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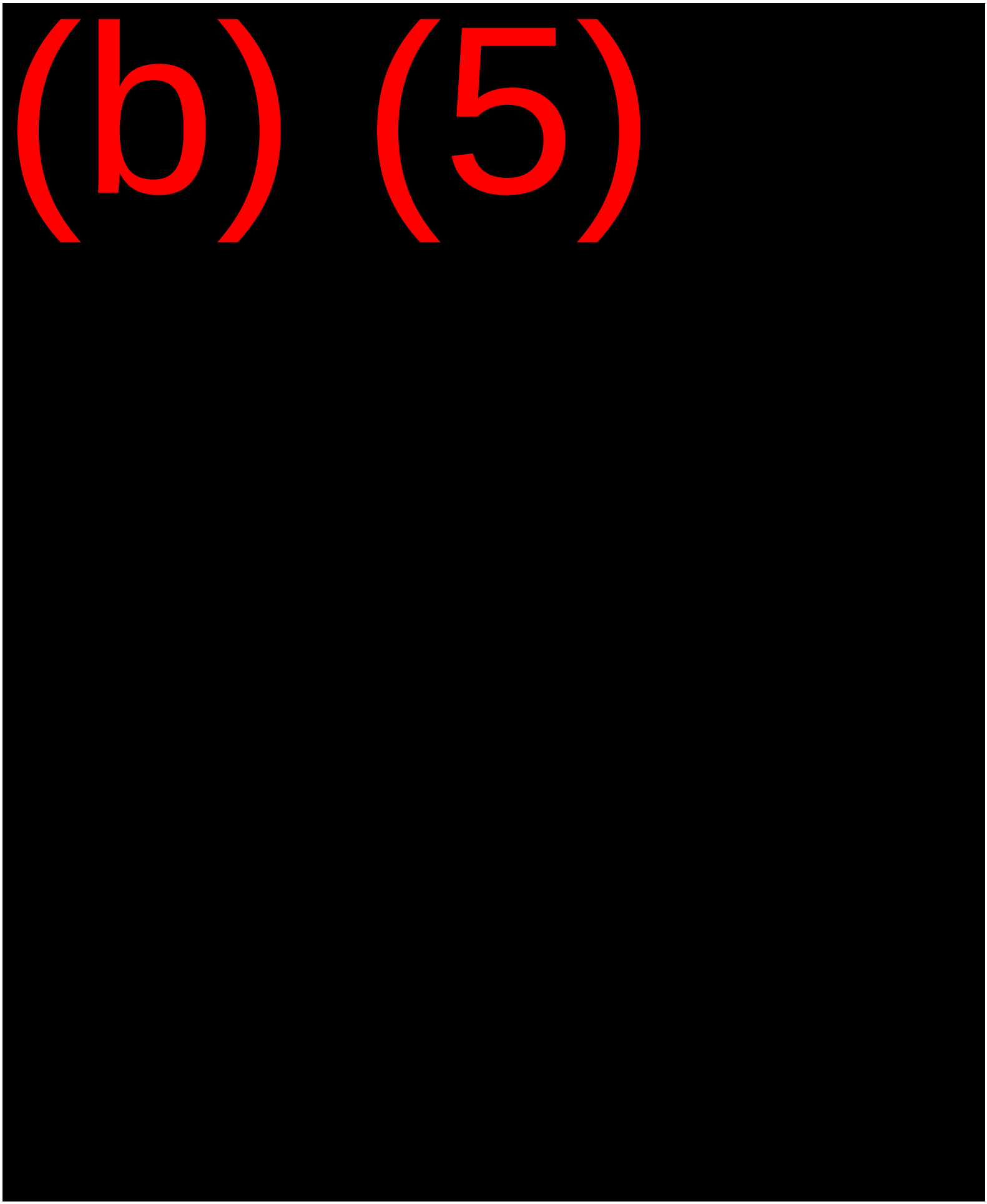
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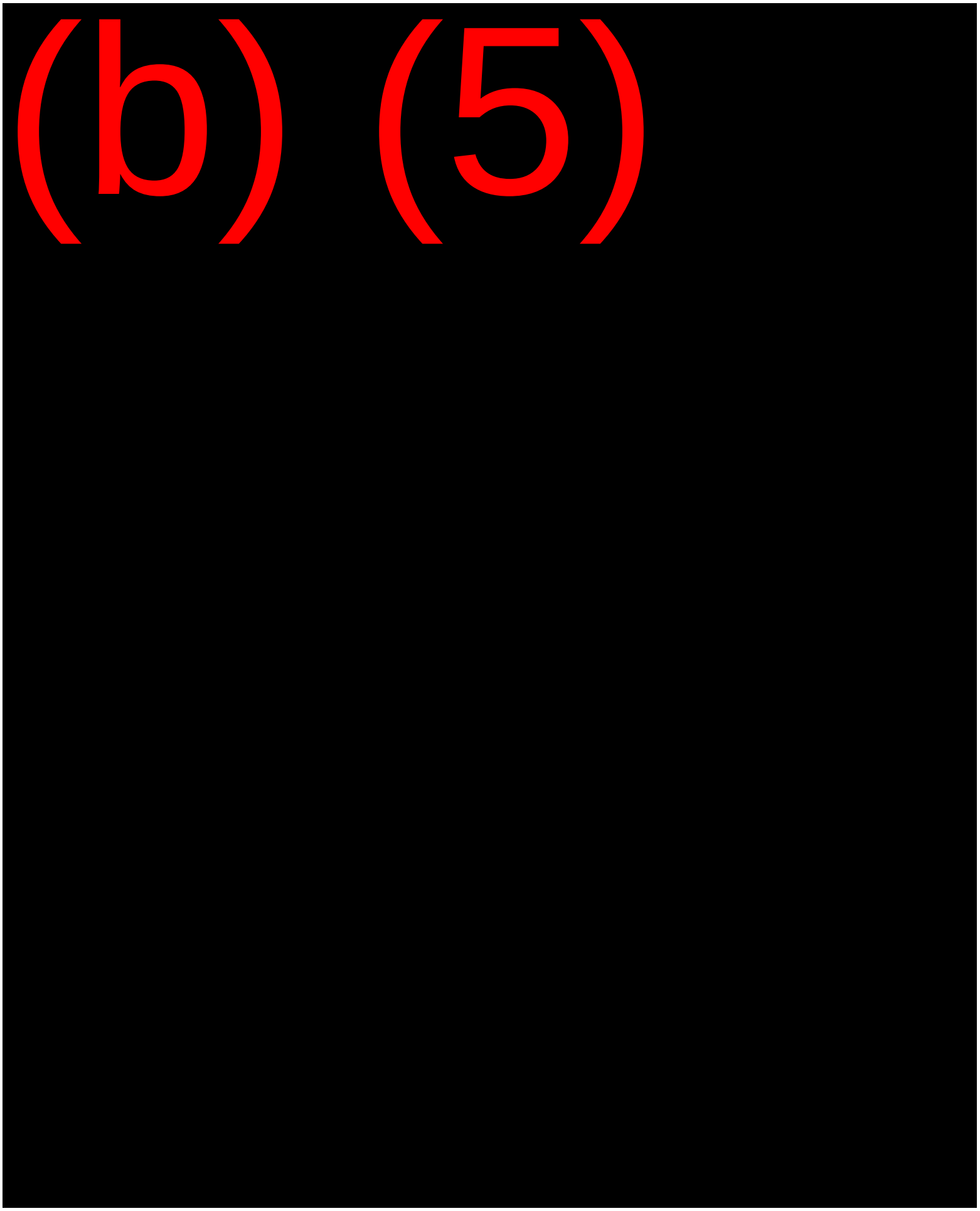
[1] https://www.epa.gov/research/administrator-memo-prioritizing-efforts-reduce-animal-testing-september-10-2019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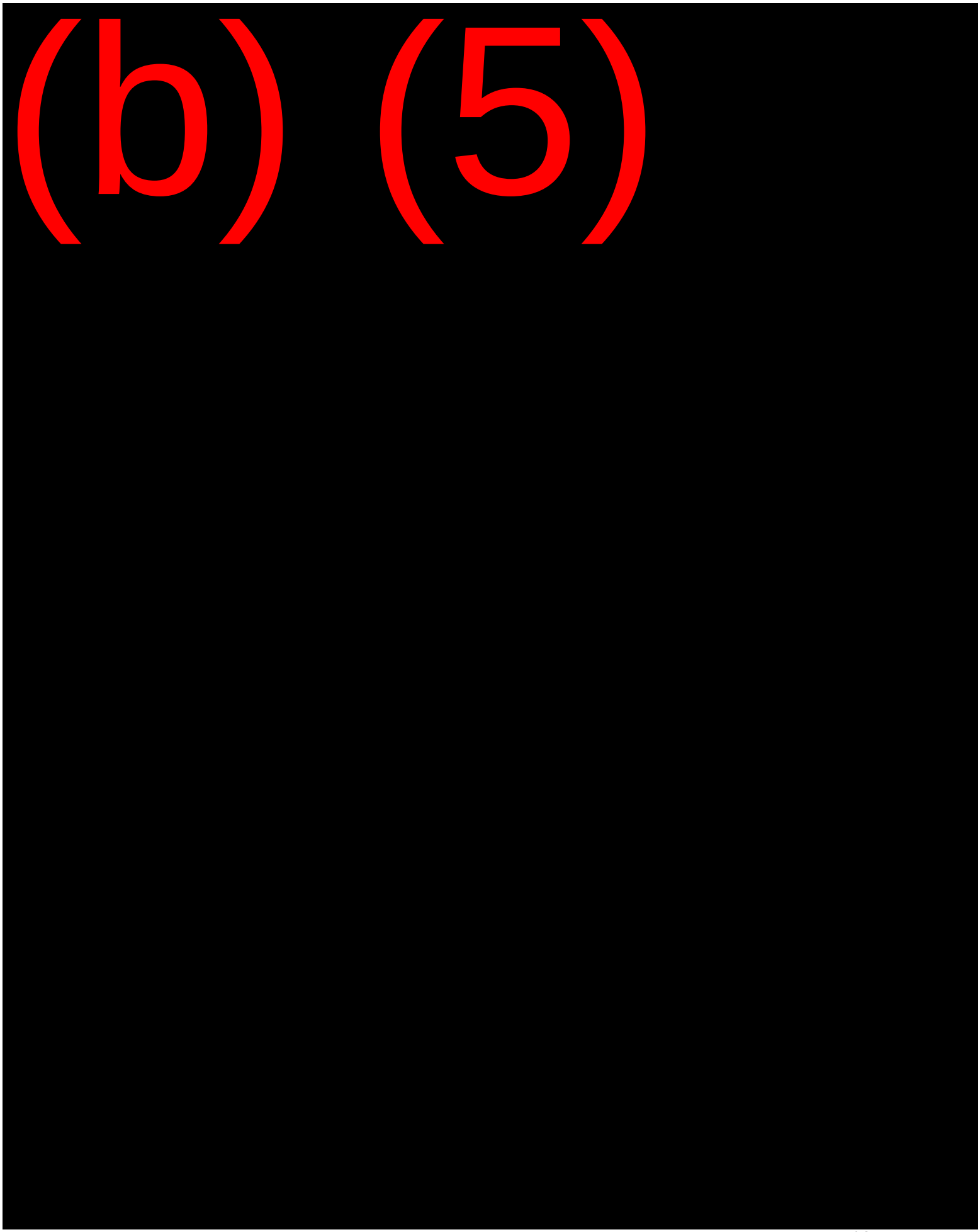
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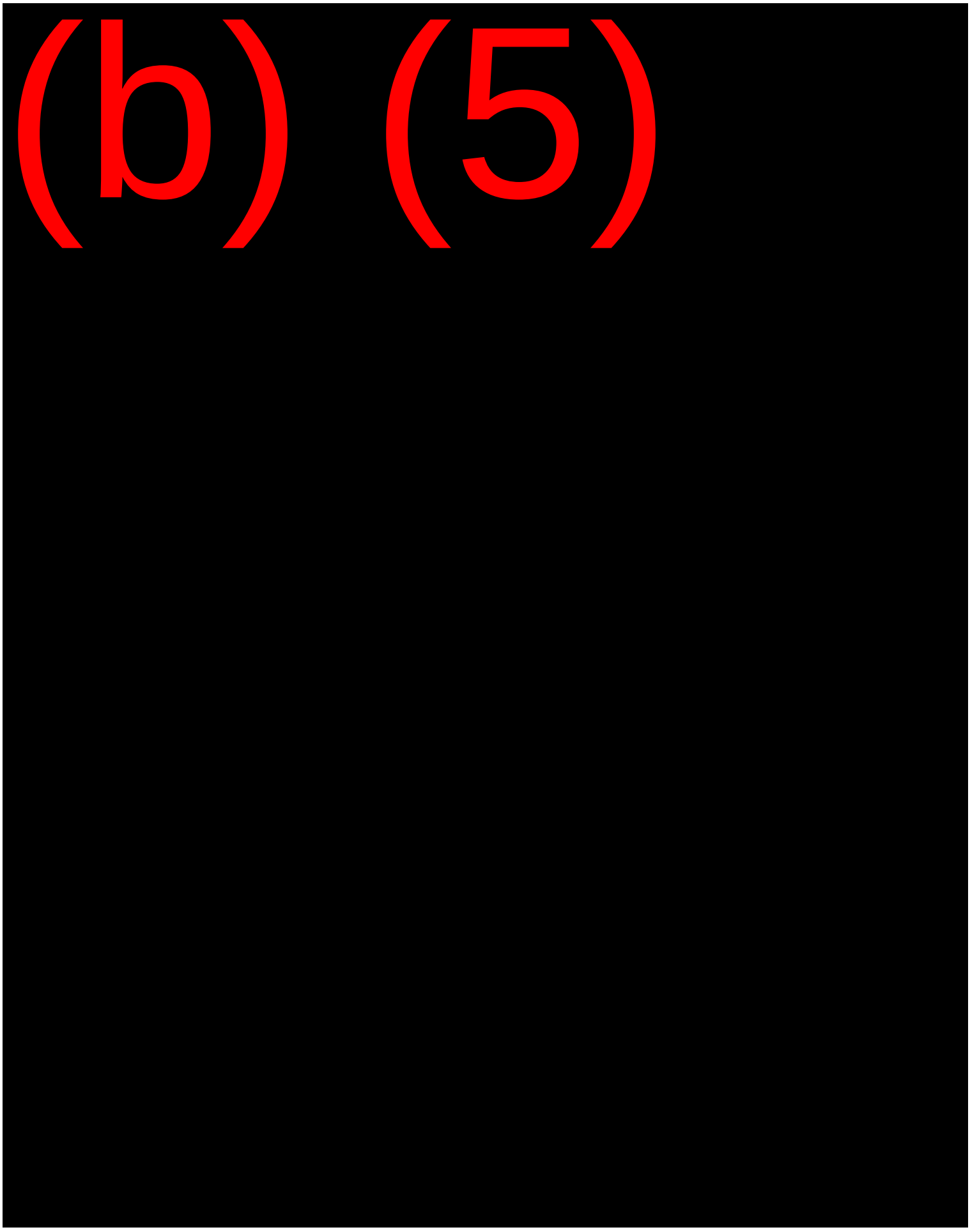
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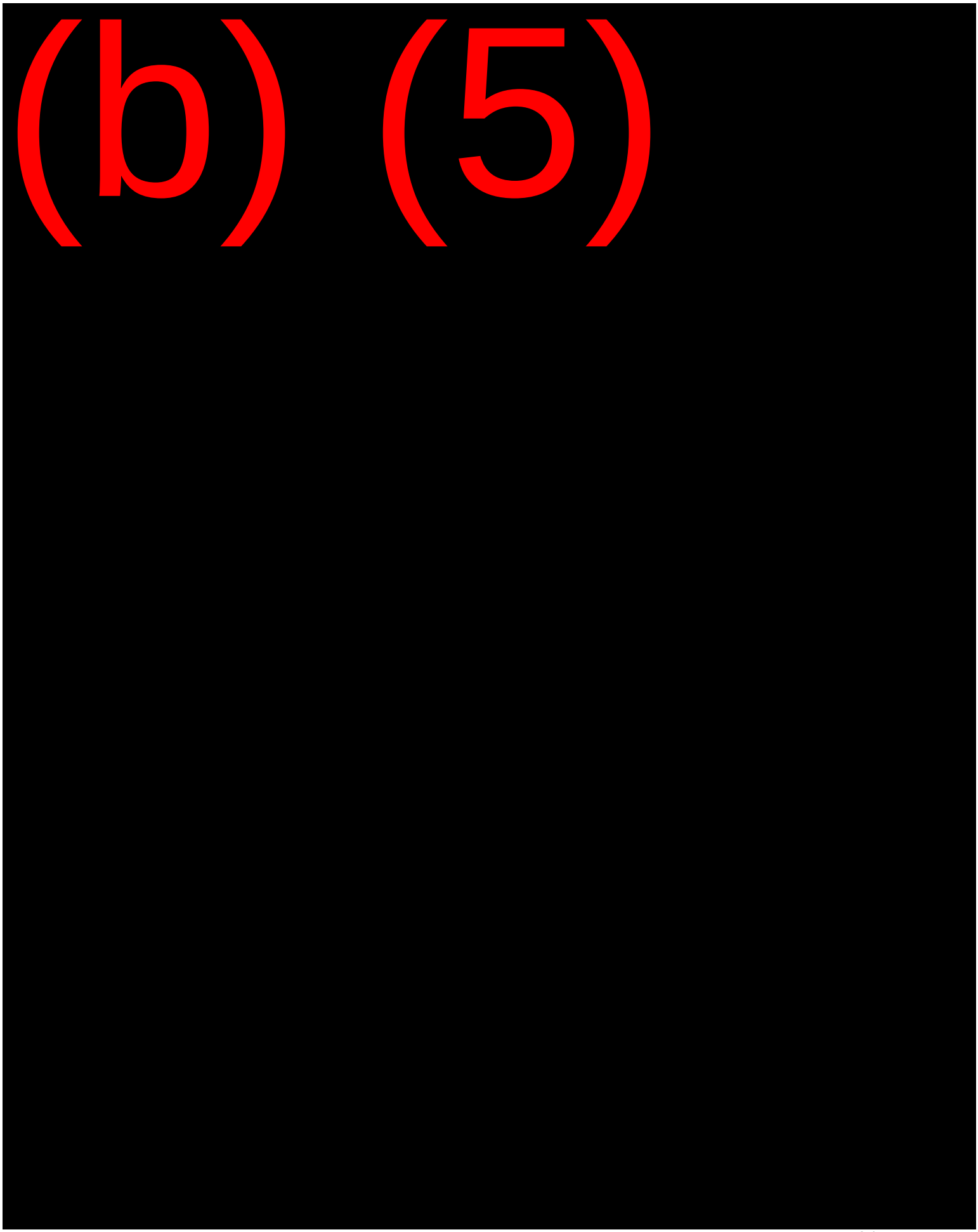
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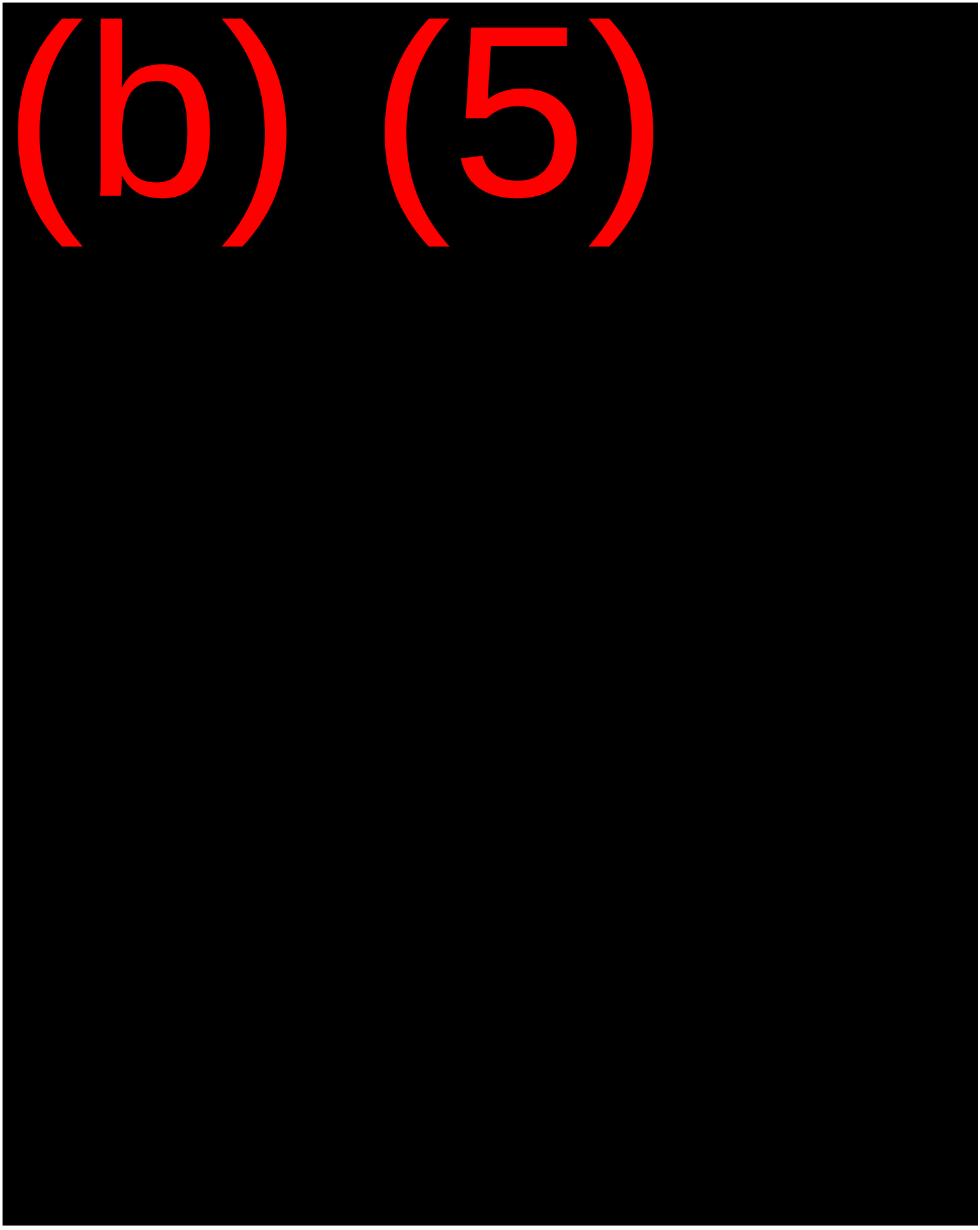
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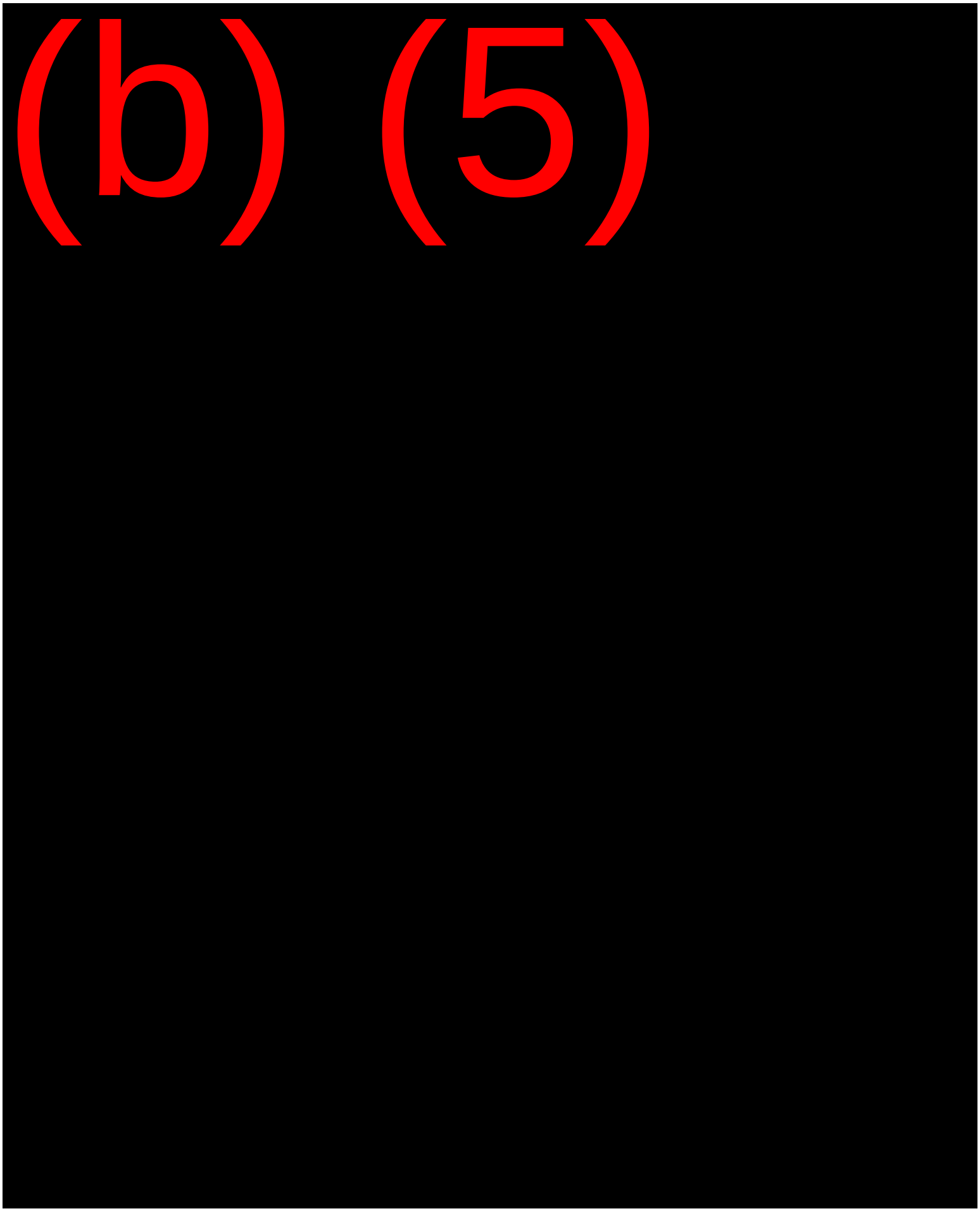
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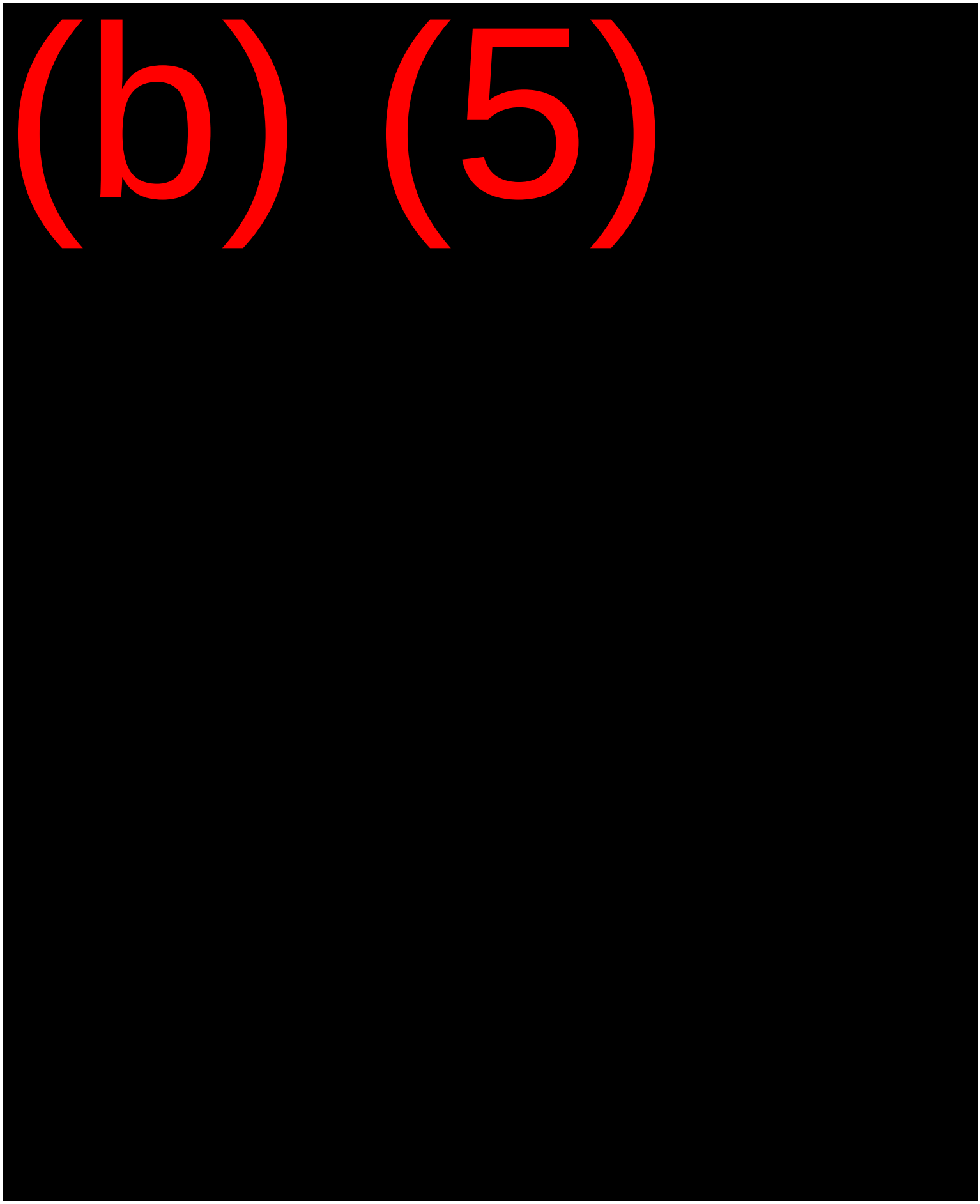
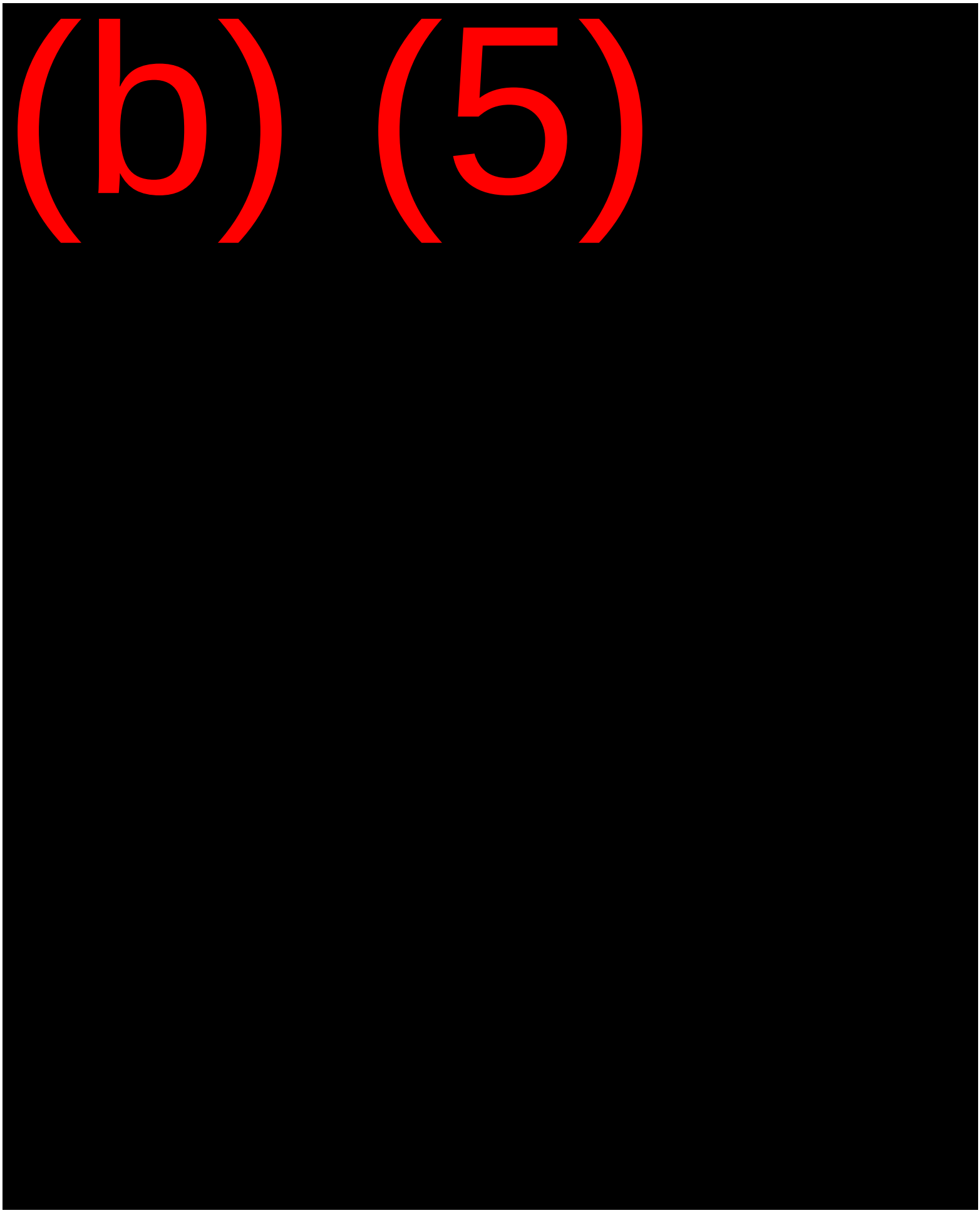



[2] https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf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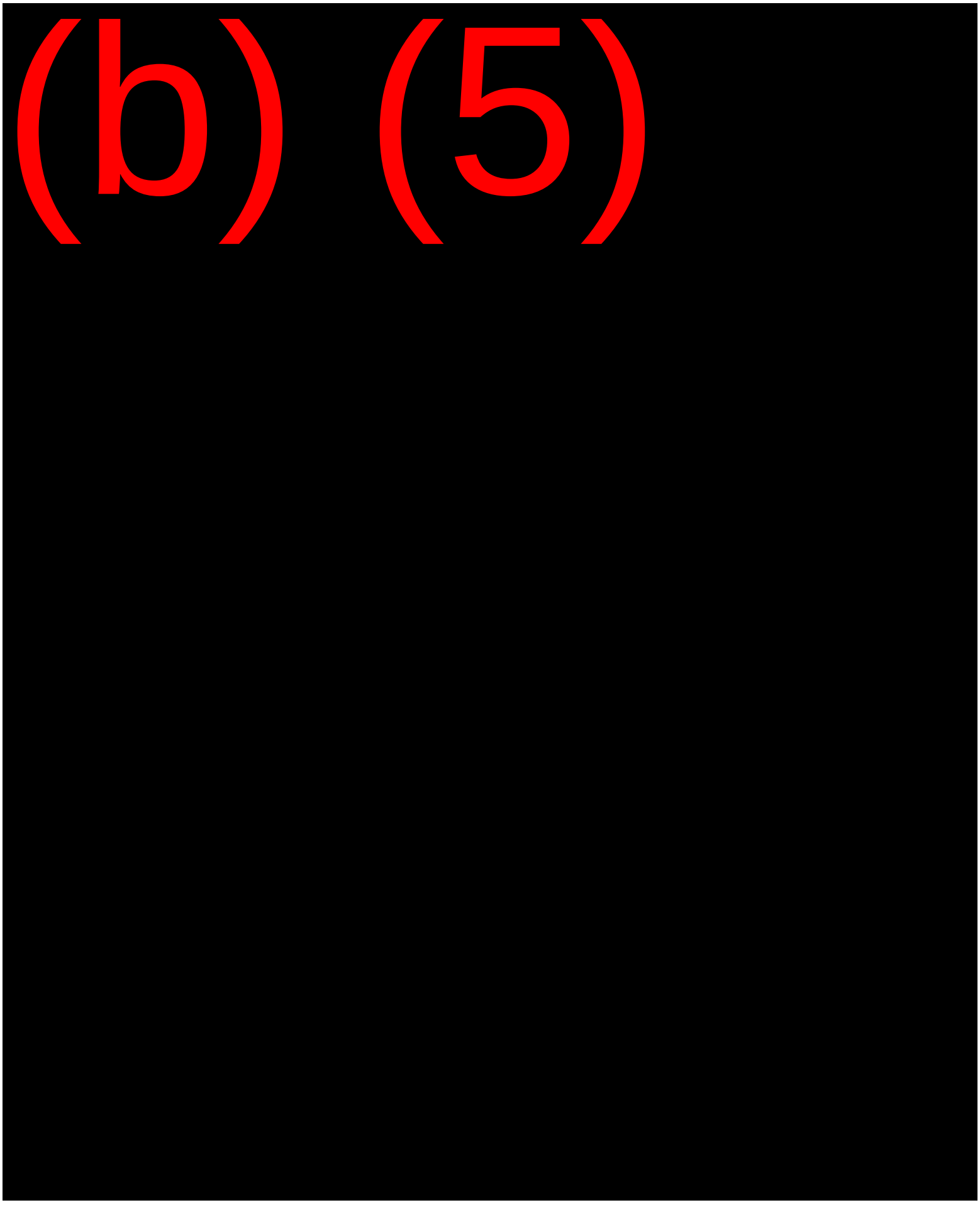
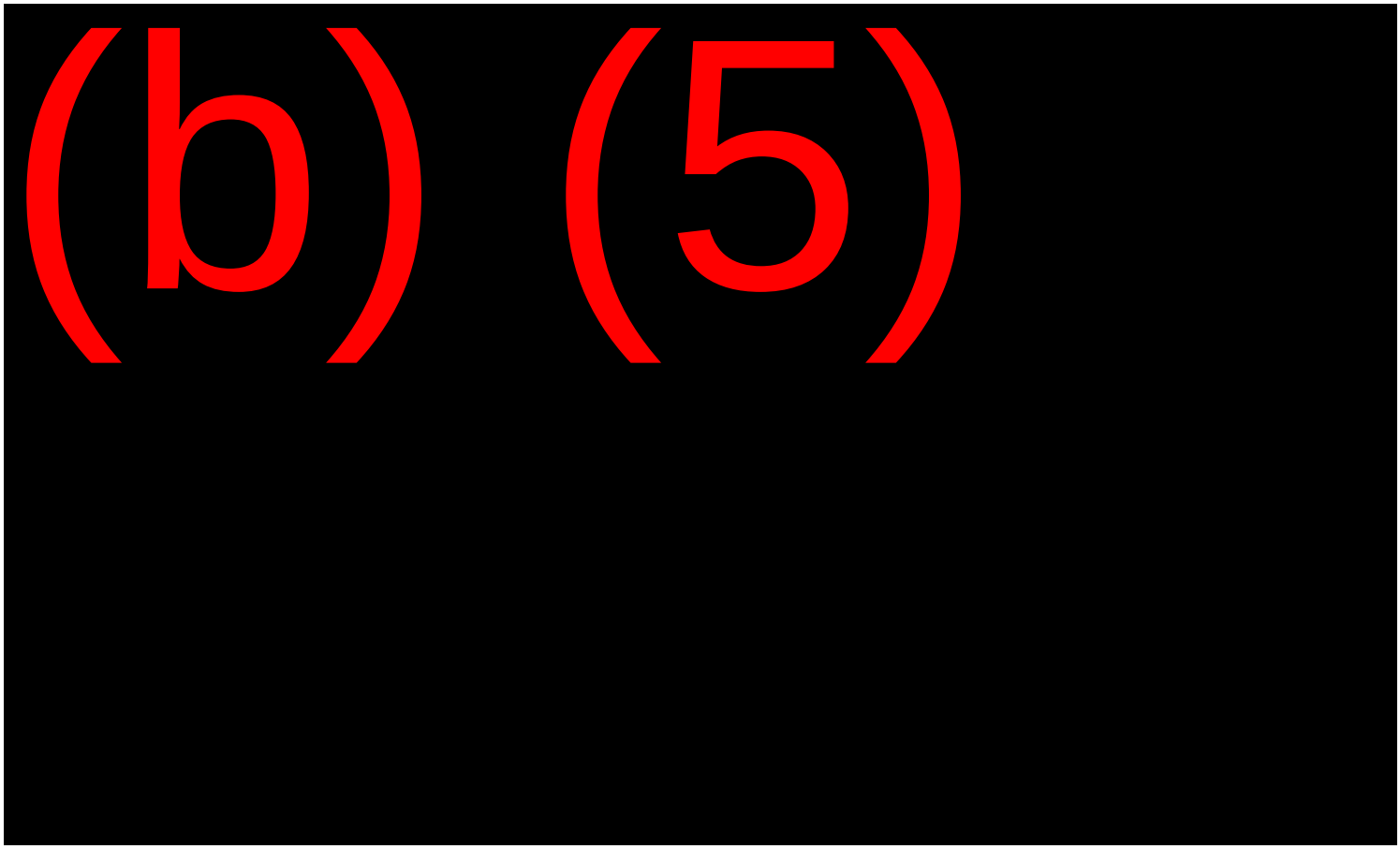

(b) (5)

[redacted]

[3] U.S. EPA. (2018). Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program. Office of Chemical Safety and Pollution Prevention, document no. EPA-740-R1-8004 https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf


(b) (5)

## Appendix 1 – Attendees

| Subgroup 1: Baseline, measurements, and reporting mechanisms to track progress | |
|---|---|
| **Name** | **Affiliation** |
| Evisabel Craig | U.S. EPA, OPP |
| David Diaz-Sanchez *(Subgroup Lead)* | U.S. EPA, ORD |
| Jaimie Graff | U.S. EPA, ORD |
| Chantel Nicolas | U.S. EPA, OPPT |
| Kristan Markey | U.S. EPA, OSCP |
| Martin Phillips | U.S. EPA, OPPT |
| Rachel McGill | *ICF Notetaker* |

| Subgroup 2: State of the science in NAM development | |
|---|---|
| **Name** | **Affiliation** |
| Jone Corrales | U.S. EPA, OPPT |
| Allison Crimmins | U.S. EPA, OAR |
| Jeff Frithsen | U.S. EPA, ORD |
| Sarah Gallagher | U.S. EPA, OPPT |
| Maureen Gwinn *(Subgroup Lead)* | U.S. EPA, ORD |
| Joshua Harrill | U.S. EPA, ORD |
| Anna Lowit | U.S. EPA, OPP |
| Kathleen Raffaele | U.S. EPA, OLEM |
| Bill Wooge* | U.S. EPA, OSCP |
| Steven Black | *ICF Notetaker* |

** Did not attend*

| Subgroup 3: Variability and uncertainty of existing models and NAMs in the context of validation | |
|---|---|
| **Name** | **Affiliation** |
| David Bussard | U.S. EPA, ORD |
| Mike DeVito | U.S. EPA, ORD |
| Kellie Fay | U.S. EPA, OPPT |
| Stiven Foster | U.S. EPA, OLEM |
| William Irwin | U.S. EPA, OPPT |
| Samantha Jones | U.S. EPA, ORD |
| Ed Odenkirchen | U.S. EPA, OPP |
| Katie Paul Friedman | U.S. EPA, ORD |
| Monique Perron *(Subgroup Lead)* | U.S. EPA, OPP |
| Kathleen Clark | *ICF Notetaker* |

| Subgroup 4: Application under various statutes (FIFRA, TSCA, etc.) and updating statutory requirements | |
|---|---|
| **Name** | **Affiliation** |
| Betsy Behl* | U.S. EPA, OW |
| Susan Burden | U.S. EPA, ORD |
| Dan Chang | U.S. EPA, ORD |
| Louis D'Amico | U.S. EPA, ORD |
| Colleen Flaherty* | U.S. EPA, OW |
| Bob Hetes* | U.S. EPA, OAR/QAQPS |
| Jan Matuszko | U.S. EPA, OPP |
| Shannon Rebersak | U.S. EPA, OGC |
| Louis (Gino) Scarano *(Subgroup Lead)* | U.S. EPA, OPPT |
| Todd Stedeford | U.S. EPA, OPPT |
| Alessandria Schumacher | *ICF Notetaker* |

** Did not attend*

| Subgroup 5: Communications and outreach | |
|---|---|
| **Name** | **Affiliation** |
| Susanna Blair | U.S. EPA, OCSPP/OPPT |
| Anna Champlin | U.S. EPA, ORD |
| Cheryl Dunton | U.S. EPA, OCSPP |
| Monica Linnenbrink *(Subgroup Lead)* | U.S. EPA, ORD |
| Steven Snyderman | U.S. EPA, OCSPP/OPP |
| Megan Rooney | *ICF Notetaker* |

| Other Attendees – Not Assigned to a Subgroup | |
|---|---|
| **Name** | **Affiliation** |
| David Dunlap | U.S. EPA, ORD |
| Alexandra Dunn | U.S. EPA, OCSPP |
| Tala Henry | U.S. EPA, OPPT |
| Sarah Stillman | U.S. EPA, OCSPP |
| Rusty Thomas | U.S. EPA, ORD |

## Appendix 2 – Acronyms

| Acronym | Full Name |
|---|---|
| APA | Administrative Procedures Act |
| ATAEPI | Analysis of TSCA Available, Expected and Potentially Useful Information |
| CAA | Clean Air Act |
| CBI | Confidential Business Information |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CWA | Clean Water Act |
| EFED | Environmental Fate and Effects Division |
| ESA | Endangered Species Act |
| FACA | Federal Advisory Committee Act committee |
| FDA | U.S. Food and Drug Administration |
| FFDCA | Federal Food, Drug, and Cosmetic Act |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| GAO | U.S. Government Accountability Office |
| IATA | Integrated Approaches to Testing and Assessment |
| ICCVAM | Interagency Coordinating Committee on the Validation of Alternative Methods |
| IRIS | Integrated Risk Information System |
| IVIVE | In vitro to in vivo extrapolation |
| LLNA | Local lymph node assay |
| MCL | Maximum Contaminant Level |
| OAR | Office of Air and Radiation |
| OCSPP | Office of Chemical Safety and Pollution Prevention |
| OECD | Organisation for Economic Co-operation and Development |
| OGC | Office of the General Council |
| OLEM | Office of Land and Emergency Management |
| OPP | Office of Pesticide Programs |
| OPPT | Office of Pollution Prevention and Toxics |
| ORD | Office of Research and Development |
| OW | Office of Water |
| PMN | Pre-manufacture Notice |
| PPRTV | Provisional Peer-Reviewed Toxicity Values |
| QAPP | Quality Assurance Project Plan |
| QSARs | Quantitative Structure Activity Relationships |
| RAF | Risk Assessment Forum |
| RCRA | Resource Conservation and Recovery Act |
| REACH | Registration, Evaluation, Authorization and Restriction of Chemicals |
| SACC | Science Advisory Committee on Chemicals |
| SDWA | Safe Drinking Water Act |
| SNAP | Significant New Alternatives Policy |
| SNUR | Significant New Use Rule |
| STPC | Science and Technology Policy Council |
| StrAP | Strategic Action Plan |
| TSCA | Toxic Substances Control Act |